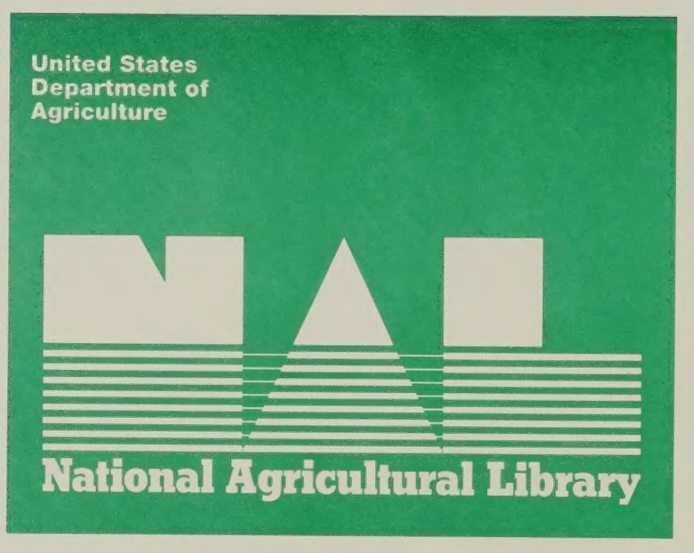

United States
Department of
Agriculture

Animal and
Plant Health
Inspection
Service

Biotechnology,
Biologics, and
Environmental
Protection

VETERINARY BIOLOGICS NOTICE

Subject: Risk Analysis for Veterinary Biologics

To: Biologics Licensees and Permittees
Director, National Veterinary Services Laboratories
Directors, VS Regions
Deputy Director, Veterinary Biologics Field Operations, BBEP
Area Veterinarians in Charge, VS

The enclosed document outlines the process used by APHIS to ensure the safety of new experimental veterinary biologics. This document is provided for your information.

Sincerely,

John H. Payne, Ph.D.
Acting Director

Enclosure

Risk Analysis for Veterinary Biologics

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February 4, 1994

TABLE OF CONTENTS

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ACRONYMS

AF	Animal Facility
APHIS	Animal and Plant Health Inspection Service (USDA)
BBEP	Biotechnology, Biologics, and Environmental Protection (USDA, APHIS)
BL	Biosafety Levels for Veterinary Biologics Containment Categories
C	Certain (Certainty Ratings)
CBI	Confidential Business Information
CDC	Center for Disease Control
CH	Consequence High (Value Ratings)
CL	Consequence Low (Value Ratings)
CM	Consequence Medium (Value Ratings)
CEQ	U.S. Council on Environmental Quality
CFR	Code of Federal Regulations
EA	Environmental Assessment
EIS	Environmental Impact Statement
FOIA	Freedom of Information Act
FONSI	Finding of No Significant Impact
GDP	Good Developmental Practices
HHS	Health and Human Services
IBC	Institutional Biosafety Committee
LH	Likelihood High (Value Ratings)
LL	Likelihood Low (Value Ratings)
LM	Likelihood Medium (Value Ratings)
LS	Large Scale Production
MC	Moderately Certain (Certainty Ratings)
MS	Master Seed
NEPA	National Environmental Policy Act
NIH	National Institute of Health
NRC	National Research Council
NVPO	National Vaccine Program Office
NVSL	National Veterinary Services Laboratories
OECD	Organization for Economic Co-Operation and Development
U	Uncertain (Certainty Ratings)
USDA	United States Department of Agriculture
VB	Veterinary Biologics Staff (USDA, APHIS, BBEP)
VSTA	Virus-Serum-Toxin Act of 1913

Risk Analysis for Veterinary Biologics

I. Introduction

A. Veterinary Biologics Risk Analysis Process

The veterinary biologics risk analysis process is used by the Animal and Plant Health Inspection Service (APHIS) to ensure the safety of new experimental veterinary biologics. It is a multi-factorial approach to risk assessment: risks to animals, public health, and the environment are assessed. The risk analysis process includes a risk assessment, risk management recommendations, and procedures for communicating risk (Table 1, Page 2). The standard definition of risk is used: Risk equals the likelihood of an adverse event occurring and the consequences if that adverse event occurs. A comprehensive scientific analysis, peer review, public notification, and documentation of the decision-making process is required. This approach is consistent with accepted standards for conducting risk analysis (1,2,3).

The risk analysis for veterinary biologics centers on the safety characteristics of the vaccine microorganism and the environment in which the research is to be performed. The safety characteristics of the vaccine microorganism are based on specific empirical data and established scientific information. This information is provided by the applicant when completing the appropriate Veterinary Biologics Summary Information Format (see Section II, Page 6).

The risk analysis model presented in this document is specific to Veterinary Biologics (VB), APHIS. The risk approach developed for VB is a hybrid of various risk outlines taken from the risk assessment literature, workshops, and risk projects relating to non-indigenous organisms. Foremost was the U.S. Council on Environmental Quality (CEQ) guide to principles and methods for analyzing health and environmental risks (1), the National Research Council (NRC) workshops and meetings for the development of ecological risk assessments (3), and the thesis by Morris A. Levin and Harlee S. Straus on risk assessment in genetic engineering (4). The basic approach and philosophy used by VB in the development of the VB risk analysis process borrows significantly from these sources.

B. Objective

The risk analysis for veterinary biologics is used by APHIS to: 1) determine whether a request to ship an experimental veterinary biologic should be approved or denied; 2) ascertain whether adequate information was provided with the request; 3) provide appropriate mitigative recommendations to reduce or eliminate potential safety risks; 4) prepare National Environmental Policy Act (NEPA) environmental documents; and 5) communicate the risk and/or level of uncertainty associated with the proposed request to the concerned public. The objective is to ensure the safety of experimental veterinary biologics. The methods used to identify and assess potential safety risks are explicitly described, and the results of the analysis are presented in a form useful for decision-making (Figure 1, Page 3). One important feature of this risk analysis is that significant effort is placed on the identification of hazards early in the risk analysis process. This is accomplished by providing industry with Veterinary Biologics Summary Information Formats in the early stages of product development.

C. Applicable Regulations

1. The Virus-Serum-Toxin Act

The authority for the regulation of veterinary biologics in the United States is

Table 1: Veterinary Biologics Risk Analysis

VETERINARY BIOLOGICS
RISK ANALYSIS

I. Objective/Proposal

II. Characterization of the vaccine microorganism

- A. Microbiological/Molecular properties
- B. Biological properties

III. Risk assessment

- A. Hazard identification
  1. Animal safety
  2. Public health safety
  3. Environmental safety
- B. Release assessment
- C. Risk characterization

IV. Risk management

- A. Contained study
- B. Environmental release

V. Risk communication

- A. Standard review
- B. Special review

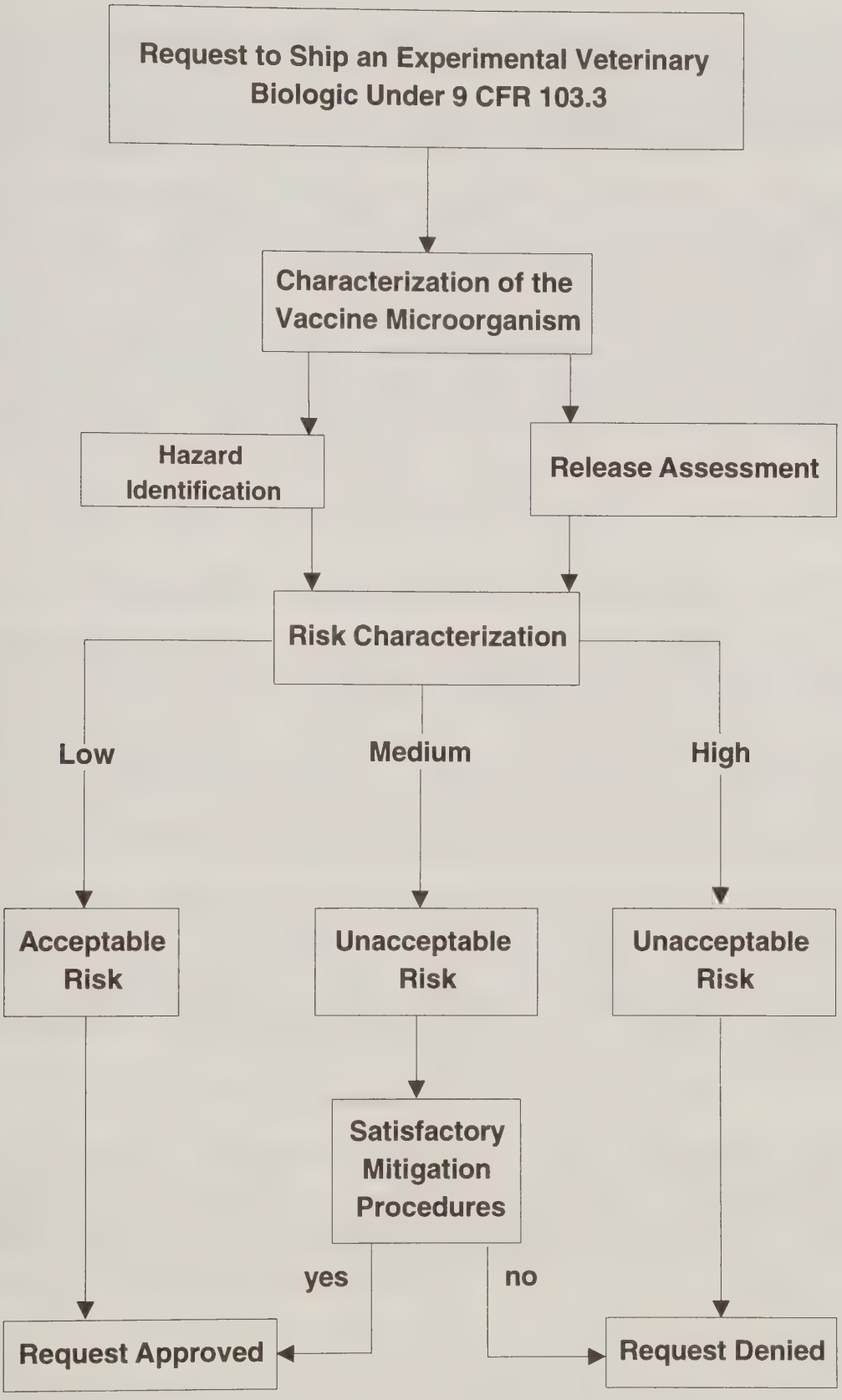

Figure 1: Veterinary Biologics Risk Analysis Process

provided in the Virus-Serum-Toxin Act (VSTA) of 1913 (21 U.S.C. 151-159). VSTA was enacted by congress to prevent the importation and interstate shipment of worthless, contaminated, dangerous, or harmful veterinary biological products. VSTA was amended by the Food Security Act of 1985 to expand this authority to include all products shipped into, within, or from the United States.

The United States Department of Agriculture (USDA) is charged with the mandate to promulgate regulations and procedures consistent with VSTA to ensure that veterinary biologics are pure, safe, potent, and efficacious. VB, Biotechnology, Biologics, and Environmental Protection (BBEP), APHIS, administers the pursuant regulations, Title 9, Code of Federal Regulations (9 CFR), Parts 101 to 118.

Experimental veterinary biologics are subject to the provisions of 9 CFR, Part 103. Requests to ship experimental veterinary biologics must meet the conditions outlined in Section 103.3. The Veterinary Biologics Risk Analysis Process is used by APHIS to evaluate such requests when the proposal involves the release of experimental biologics from laboratory containment. It is also used to evaluate the issuance of a U.S. Veterinary Biological Product License (9 CFR 102.1), when such action would result in conditions that are different than those evaluated prior to licensure of the product; e.g., use of the product by veterinarians in small field tests verses unrestricted use once the product is licensed.

2. The National Environmental Policy Act

Upon receipt of a request to ship an experimental veterinary biologic, APHIS must determine whether the provisions of the National Environmental Policy Act (NEPA) of 1969 are triggered. NEPA (42 U.S.C. 4371) procedures are triggered whenever there is a proposed Federal action with a potential for significant impact upon the environment. APHIS approval to release an experimental veterinary biologic into the environment may be such a federal action. NEPA procedures are intended to facilitate the federal decision-making process by requiring an analysis of alternatives to the proposed federal action, a comprehensive consideration of the environmental effects of the proposed activity, and involvement of the public in the decision-making process prior to making a decision.

The Council on Environmental Quality (CEQ) regulations under 40 CFR, Parts 1500 to 1508, implement Section 102(2) of NEPA. According to these regulations, actions by a government agency such as APHIS may fall into one of four categories: (1) actions which are exempt due to categorical exclusion; (2) actions which are covered by an existing environmental document; (3) actions which require preparation of an Environmental Assessment; or (4) actions which require preparation of an Environmental Impact Statement.

3. The Freedom of Information Act

The Freedom of Information Act (5 U.S.C. 552) was enacted by Congress to give the public limited access to government records. By law, information in the possession and control of APHIS that qualifies as a record and that is not exempt from disclosure under the Act must be made available upon written request. APHIS must respond to a request within 10 working days. Confidential business information, as defined by the Act, as well as trade secrets from the private sector, are exempt.

II. Characterization of the Vaccine Microorganism

The first phase in the risk analysis process is to characterize the vaccine microorganism. The objective is to identify the safety characteristics of the experimental biologic.

A. Safety Studies

The safety characteristics of experimental veterinary vaccines are identified using established safety studies: purity tests; tissue culture studies; laboratory animal studies; host animal safety studies; reversion to virulence studies; and field safety studies. The majority of these studies are routinely conducted in support of product license applications for veterinary biologics. These studies provide sufficient information to ensure that the product is safe for the intended species and that it will not adversely affect the environment upon its release from containment. Some overlap purposefully exists to assess safety under different conditions.

B. Target Objectives

In order to properly characterize the vaccine microorganism, the following target objectives should be met:

1. Differentiate the vaccine microorganism from the parental microorganism (e.g., identify the presence of genetic markers such as auxotrophic mutant, temperature-sensitive mutant, etc.);

2. Confirm the identity of the master seed (MS) microorganism (e.g., as described in Bergey's Manual of Determinative Bacteriology for bacterial microorganisms);

3. Verify the genotypic and/or phenotypic stability of the MS microorganism in production (i.e., at the MS and the MS + 5 or highest passage level);

4. Identify the virulent properties of the vaccine microorganism, if any;

5. Verify the absence of pathogenic extraneous agents in the final product;

6. Examine the genotypic and phenotypic stability of the vaccine microorganism in the host animal;

7. Evaluate changes in the tissue tropism of the vaccine microorganism from that of the parental strain;

8. Assess the shed/spread capabilities and host/range specificity of the vaccine strain;

9. Consider the effect of potential horizontal gene transfers and/or recombination events, where appropriate;

10. Identify the effect of overdosing;

11. Assess the survivability of the vaccine microorganism in the environment.

The veterinary biologics industry is encouraged to provide this information by completing the appropriate Summary Information Format.

C. Summary Information Formats

Summary Information Formats specify the relevant safety information to submit to VB in support of product license applications for new veterinary biologics. These regulatory guidelines were designed to assist industry identify the safety characteristics of experimental biologics. VB recognizes that because of their inherent complexity, the regulation of biologics does not easily conform to checklists or rigid guidelines. Some questions may not be relevant to a particular vaccine microorganism. Notwithstanding, research objectives are often inconsistent with regulatory objectives, resulting in research data that are frequently insufficient to satisfy licensing requirements. This is especially true of recombinant vaccines, most of which are still in the experimental stage. Accordingly, these regulatory guidelines give the biologics industry a common set of scientific principles that can be used to successfully characterize an experimental biologic. Importantly, they provide the way for including industry in the risk analysis process. Thus, VSTA and NEPA are integrated at the onset of product development; safety is considered at the very beginning.

Four Summary Information Formats are available for each category of veterinary biologics. To streamline the review process, VB supplies Summary Information Formats to applicants with instructions for completion on a computer diskette.

1. Summary Information Format for Veterinary Biologics

This Summary Information Format was designed for conventional vaccines that contain live microorganisms (see Appendix A, Page 24). The characterization of the vaccine microorganism is based on its microbiological and biological properties, and those of the parental microorganism from which the vaccine strain was derived.

2. Summary Information Format for Category I Veterinary Biologics

This Summary Information Format was designed for inactivated recombinant microorganisms (see Appendix B, Page 25). Inactivated microorganisms are killed and therefore no longer viable. Inactivated recombinant microorganisms are used in the manufacture of killed vaccines, sub-unit vaccines, or diagnostic kits. The characterization of the recombinant microorganism centers on its molecular properties, as well as those of the recipient microorganism, and any deleted or donor genes. Obviously, it is not anticipated that inactivated microorganisms and their components will pose a threat to the environment. However, the veterinary biologics risk analysis process is used to ensure that the recombinant microorganism is properly characterized and inactivated.

3. Summary Information Format for Category II Veterinary Biologics

This Summary Information Format was designed for live microorganisms that contain gene deletions and/or heterologous marker genes (see Appendix C, Page 27). The characterization of the gene-deleted microorganism is based on the molecular and biological properties of the vaccine microorganism. The microorganism receiving the genetic modifications (i.e., the recipient microorganism) is also characterized.

4. Summary Information Format for Category III Veterinary Biologics

This Summary Information Format was designed for live expression vectors that

contain heterologous genes for immunizing antigens and/or other immune stimulants (see Appendix D, Page 29). The molecular and biological properties of the recipient, the donor, and the recombinant microorganisms are identified. The characterization of the donor microorganisms includes the properties of the structural genes and their regulatory elements.

III. Risk Assessment

The risk assessment conducted by VB is a judgmental process. It is based on the best available science. The risk assessment includes the identification of safety hazards, a release assessment, and the characterization of safety risks to animals, public health, and the environment. It is used to determine whether risks are associated with the specific proposal to test and/or release an experimental veterinary biologic from containment, and characterizes the degree of uncertainty associated with the proposal.

Risk means many different things to different people; risk is often subject to different interpretations, depending on how the risk is communicated and perceived. VB uses the standard definition of risk: Risk equals the likelihood of an adverse event occurring and the consequences if that adverse event occurs. An adverse event is defined as a safety hazard to animals, public health, or the environment. A safety hazard is defined as a danger or peril; the absence or lack of predictability associated with an event; or an unexpected or unpredictable detrimental event.

Please note that VB risk assessments are based on the information submitted by the applicant. However, additional information may be incorporated by the VB risk analyst, or as a result of peer review (see Section V, Page 17). The significance of "no information" is assessed along with the available information.

A. Hazard Identification

The first step in the risk assessment consists of identifying all possible safety hazards to animals, public health, and the environment. The identification of hazards is based on the safety characteristics of the vaccine microorganism. This information is obtained from the results of safety studies conducted by the applicant and the appropriate scientific literature.

At this stage, the risk analyst must determine whether safety hazards exist, and not conclude that a risk necessarily exists. Thus, VB risk analysts must dissociate themselves from the outcome of the risk assessment and focus on the characteristics of the vaccine microorganism to ensure that all possible safety hazards are identified. To standardize this process, specific issues have been identified for the VB risk analyst, recognizing that the subject of safety for veterinary biologics is broad and complex and that additional or alternative issues may need to be considered as different proposals are evaluated (see Appendix E, Page 31).

B. Release Assessment

The safety characteristics of the vaccine microorganism must be evaluated within the context of the target environment. Thus, the release assessment consists of a comprehensive evaluation of the proposed release so as to determine: 1) the location and characteristics of the release site; 2) the test dose and total amount of the experimental biologic to be used in the proposed study; 3) the frequency and duration of exposure to the test material; 4) potential escapes into occupational, residential, or outdoor environments; and 5) the individuals, populations, or ecosystems that will be, or may be, exposed to the experimental biologic.

For the purpose of VB risk assessments, proposed studies with live experimental vaccine microorganisms are classified as either contained studies or environmental releases. A *Contained study* is defined as an experiment in laboratory containment or physically contained animal facilities. An *Environmental Release* refers to the release of the vaccine microorganism to the

accessible environment. The *Accessible Environment* is defined as the environment that can be reached by the vaccine microorganism and its progeny.

Summary Information Formats are available for each type of study. VB supplies these Summary Information Formats to applicants with instructions for completion on a computer diskette.

1. Summary Information Format for Contained Studies

This Summary Information Format was specifically designed for contained studies (see Appendix F, Page 32). Contained studies enable licensees to more fully evaluate the safety characteristics of live experimental vaccines prior to their release into the environment. Thus, sufficient information must be provided to ensure that the contained study will not result in the release of the experimental vaccine microorganism.

2. Summary Information Format for Environmental Releases

The progression to determine the safety characteristics of an experimental vaccine microorganism eventually requires research involving planned introductions into the environment. This Summary Information Format identifies the information that should be supplied to VB for each planned introduction (Appendix G, Page 33). *Planned Introductions Into the Environment* refers to the deliberate release of live microorganisms from contained facilities to the environment. Differences between small-scale field tests and commercial releases are considered in the release assessment. VB, APHIS recommends and encourages the use of small-scale field tests, as appropriate for the experimental veterinary biologic.

C. Risk Characterization

Risk Characterization integrates the results of the hazard identification and the release assessment into a risk statement that includes: 1) a **likelihood rating**; 2) a **consequence rating**; 3) a **risk rating**; and 4) a discussion of risk. Each likelihood and consequence rating is qualified by a **Degree of certainty rating** and includes a justification for the rating. The justifications for the ratings consist of identifying the applicable sections in the hazard identification and the release assessment that support the assigned rating. The **risk rating** is based upon the likelihood, consequence, and degrees of certainty ratings.

1. Likelihood Rating

Likelihood ratings are assigned for animal safety, public health safety, and environmental safety, based on the following criteria:

Low	=	An adverse event is unlikely to occur.
Medium	=	An adverse event could possibly occur.
High	=	An adverse event will most probably occur.

2. Consequence Rating

Consequence ratings are also assigned for animal safety, public health safety, and environmental safety, based on the following criteria:

Low	=	The consequence if the adverse event occurs is not severe (the adverse event is self-limiting and would have negligible impact).

Medium	=	The consequence if the adverse event occurs is moderately severe (the adverse event will have an impact, but is not permanent, and can be treated).
High	=	The consequence if the adverse event occurs is severe (the adverse event will have an impact, is permanent, and cannot be treated).

3. Degree of Certainty Rating

Each likelihood and consequence rating is qualified by a degree of certainty rating that is based on the following criteria:

Certain	=	The rating is supported by direct scientific evidence.
Moderately Certain	=	The rating is supported by indirect scientific evidence.
Uncertain	=	The rating is not supported by scientific evidence.

4. Calculating the Expected Risk

Numerical values have been assigned to the likelihood, consequence, and degree of certainty ratings described above (see Table 2, Page 11). Each numerical value rating was derived from the importance placed on the rating for each category. The assigned numerical values are weighed to place emphasis on the severity of the expected risk. These values reflect the professional judgment of VB, BBEP, APHIS, USDA. To determine the expected risk, the numerical values are multiplied.

The numerical values assigned to the "*Degree of Certainty*" reflect the level of uncertainty associated with the risk ratings. The need for two different rating systems reflects the reality of how uncertainty is perceived when handing risk. A low risk with a high degree of certainty is of **less concern** than a low risk which shows a high degree of uncertainty; a high risk with a high degree of certainty is of **more concern** than a high risk which shows a high degree of uncertainty.

This is easy to understand by using an analogy about risk. A pedestrian is less likely to cross the road if (s)he is convinced (s)he is going to be hit by a car than if the pedestrian is not sure that (s)he will be hit by a car (*high risk with a high degree of certainty is of **more concern** than a high risk which shows a high degree of uncertainty*). However, the same pedestrian is more likely to cross the road if (s)he is convinced that (s)he is not going to be hit by a car than if (s)he thinks that (s)he might be hit by a car (*low risk with a high degree of certainty is of **less concern** that a low risk which shows a high degree of uncertainty*). The use of the two rating systems (one a reciprocal of the other) reflects this perception of risk.

5. Risk Ratings

The **risk ratings** are based upon the likelihood, consequence, and degrees of certainty ratings and the expected risk for each category (see Table 2, Page 11). A total of 81 rating combinations are possible; e.g., Likelihood Low-Moderately Certain, Consequence Low-Moderately Certain (see Table 3, Page 12). Each combination has been assigned a **risk rating** of low, medium, or high. The assigned ratings were weighed to place emphasis on the severity of the expected risk. Again, the severity of the risk reflects the professional judgment of VB, APHIS. The low, medium, or high **risk ratings** are defined for the purpose of

Table 2: Calculating the Expected Risk

VALUE RATINGS

Likelihood (L)

Low (L)	LL = 1.00
Medium (M)	LM = 0.50
High (H)	LH = 0.10

Consequence (C)

Low (L)	CL = 1.00
Medium (M)	CM = 0.10
High (H)	CH = 0.01

If the Likelihood rating is Medium or High and the Consequence rating is also Medium or High use *Degree of Certainty Ratings I*; for all other combinations use *Degree of Certainty Ratings II*.

Degree of Certainty Ratings I

Certain (C)	C = 0.50
Moderately Certain (MC)	MC = 0.75
Uncertain (U)	U = 1.00

Degree of Certainty Ratings II

Certain (C)	C = 1.00
Moderately Certain (MC)	MC = 0.75
Uncertain (U)	U = 0.50

EXPECTED RISK

[(likelihood) x (degree of certainty)] x [(consequence) x (degree of certainty)] = Risk Rating

---

Table 3: Risk Ratings

Risk Characterization	Expected Risk	Risk Rating
LL.C.CL.C.	1.0000	L
LL.C.CL.MC.	.7500	L
LL.MC.CL.C.	.7500	L
LL.MC.CL.MC.	.5625	L
LL.C.CL.U.	.5000	L
LL.U.CL.C.	.5000	L
LM.C.CL.C.	.5000	L
LL.MC.CL.U.	.3750	M
LL.U.CL.MC.	.3750	M
LM.C.CL.MC.	.3750	M
LM.MC.CL.C.	.3750	M
LM.MC.CL.MC.	.2813	M
LL.U.CL.U.	.2500	M
LM.C.CL.U.	.2500	M
LM.U.CL.C.	.2500	M
LM.MC.CL.U.	.1875	M
LM.U.CL.MC.	.1875	M
LM.U.CL.U.	.1250	M
LH.C.CL.C.	.1000	M
LL.C.CM.C.	.1000	M
LH.C.CL.MC.	.0750	M
LH.MC.CL.C.	.0750	M
LL.C.CM.MC.	.0750	M
LL.MC.CM.C.	.0750	M
LH.MC.CL.MC.	.0563	M
LL.MC.CM.MC.	.0563	M
LH.C.CL.U.	.0500	M
LH.U.CL.C.	.0500	M
LL.C.CM.U.	.0500	M
LL.U.CM.C.	.0500	M
LM.U.CM.U.	.0500	M
LH.MC.CL.U.	.0375	M
LH.U.CL.MC.	.0375	M
LL.MC.CM.U.	.0375	M
LL.U.CM.MC.	.0375	M
LM.MC.CM.U.	.0375	M
LM.U.CM.MC.	.0375	M
LM.MC.CM.MC.	.0281	M
LH.U.CL.U.	.0250	M
LL.U.CM.U.	.0250	M
LM.C.CM.U.	.0250	M
LM.U.CM.C.	.0250	M
LM.C.CM.MC.	.0188	M
LM.MC.CM.C.	.0188	M
LM.C.CM.C.	.0125	M
LH.U.CM.U.	.0100	M
LL.C.CH.C.	.0100	M
LH.MC.CM.U.	.0075	M
LH.U.CM.MC.	.0075	M
LL.C.CH.MC.	.0075	M
LL.MC.CH.C.	.0075	M
LH.MC.CM.MC.	.0056	M
LL.MC.CH.MC.	.0056	M
LH.C.CM.U.	.0050	M
LH.U.CM.C.	.0050	M
LL.C.CH.U.	.0050	M
LL.U.CH.C.	.0050	M
LM.U.CH.U.	.0050	M
LH.C.CM.MC.	.0038	M
LH.MC.CM.C.	.0038	M
LL.MC.CH.U.	.0038	M
LL.U.CH.MC.	.0038	M
LM.MC.CH.U.	.0038	M
LM.U.CH.MC.	.0038	M
LM.MC.CH.MC.	.0028	M
LH.C.CM.C.	.0025	M
LL.U.CH.U.	.0025	M
LM.C.CH.U.	.0025	M
LM.U.CH.C.	.0025	M
LM.C.CH.MC.	.0019	H
LM.MC.CH.C.	.0019	H
LM.C.CH.C.	.0013	H
LH.U.CH.U.	.0010	H
LH.MC.CH.U.	.0008	H
LH.U.CH.MC.	.0008	H
LH.MC.CH.MC.	.0006	H
LH.C.CH.U.	.0005	H
LH.U.CH.C.	.0005	H
LH.C.CH.MC.	.0004	H
LH.MC.CH.C.	.0004	H
LH.C.CH.C.	.0003	H

decision-making (see Figure 1 page 3), as follows:

Low	=	Acceptable risk - very little concerns are associated with the proposal (does not justify denying the proposal)
Medium	=	Unacceptable risk - moderate concerns are associated with the proposal (either identify valid mitigative procedures or deny the proposal).
High	=	Unacceptable risk - major concerns are associated with the proposal (deny the proposal).

IV. Risk Management

Risk management uses the information from the risk assessment, as well as regulatory, social, and economic realities, to determine whether the proposed release should be approved (see Figure 1, page 3). Risk management also includes the design and implementation of mitigative procedures to reduce or eliminate potential safety risks. If the safety risks to animals, public health, and the environment are low, the proposed study is approved. If the risk is high the request is denied. Requests to conduct studies that have been rated with medium risks are also denied, unless proper mitigative procedures are identified and implemented.

It must be emphasized that risk management is a separate activity that is conducted independent of the risk assessment. Thus, the social, economic, and political realities that are often part of the decision making process are excluded from the risk assessment. The risk assessment seeks to identify and characterize safety risks. Risk management seeks to determine what action should be implemented to ensure that the proposed study will be conducted safely.

Because safety considerations can be significantly different for each study, it is imperative that risk management recommendations be based on a risk assessment. Although several safety guidelines for the deliberate release of genetically modified microorganisms are available, no comprehensive guidelines have been published for vaccines. The following outlines some of the procedures and guidelines that are collectively used by VB in mitigating safety risks for either contained studies or environmental releases.

A. Contained Studies

Risk management for contained studies should center on the assignment of biosafety levels, and the identification of mitigative procedures that are specific for the proposed study. For contained studies, VB relies on the expertise of the local Institutional Biosafety Committee (IBC). Thus, the IBC is responsible for assigning the appropriate biosafety levels, and the certification of the animal facilities. If an IBC has not been established, or if requested by the applicant or local authorities, VB conducts a risk assessment, assigns biosafety levels, and identifies mitigative procedures for the proposed study. Biosafety levels and mitigative procedures are based on the results of the risk assessment.

VB assigns biosafety containment levels for veterinary biologics using a three-stage review process. The first stage assigns a biosafety level to the parent microorganism. This biosafety level is assigned to three containment categories: the facilities, the containment equipment, and operational procedures. The second stage evaluates the safety characteristics of the vaccine strain itself to individually adjust the biosafety level of each containment category, if appropriate. The safety characteristics of vaccine strains are defined in the risk assessment. The third stage provides for final biosafety level adjustments based upon the proposed protocol. This process provides flexibility in determining appropriate biosafety containment levels for different situations and proposals, while minimizing potential hazards to animal and human health and the environment.

As illustrated in Table 4 (Page 15), this three-stage review process is used to assign biosafety levels for laboratory operations, production operations, and contained studies. VB assigns biosafety containment levels using procedures and standards that coincide with those established in the NIH Guidelines (9,10). These procedures implement provisions in the NIH Guidelines to individually adjust the biosafety levels of facilities, containment equipment, and operational procedures for laboratory operations, production operations, and contained

Table 4: Biosafety Levels (BL) for Veterinary Biologics Containment Categories

CATEGORY	OPERATION		
	Laboratory	Production Large Scale (LS) >10 liters	Contained release Animal facility (AF)
Facility	BL-1 BL-2 BL-3 BL-4	BL-1 BL-2 BL-3	BL-1-AF BL-2-AF BL-3-AF BL-4-AF
Containment Equipment	BL-1 BL-2 BL-3 BL-4	BL-1-LS BL-2-LS BL-3-LS	BL-1-AF BL-2-AF BL-3-AF BL-4-AF
Operational Procedures	BL-1 BL-2 BL-3 BL-4	BL-1 BL-2 BL-3	BL-1-AF BL-2-AF BL-3-AF BL-4-AF

studies in animal facilities. Biosafety level assignments for laboratory and production operations are based upon the safety characteristics of the microorganism, as defined in the risk assessment. For contained studies, the safety characteristics of new or recombinant microorganisms are considered, as well as the host animal and the protocol for the contained study. Thus, biosafety levels for containment facilities, containment equipment, and operational procedures for contained studies may be adjusted based upon the specific safety characteristics of each study.

B. Environmental Releases

Risk management for environmental releases seeks to avoid adverse environmental effects outside the primary test site. Thus, mitigative recommendations are provided to reduce or eliminate potential safety risks. The depth and breadth of risk management for environmental releases varies, depending on the biological properties of the vaccine microorganism.

Several safety guidelines are available for the deliberate release of genetically modified microorganisms. Although not written specifically for vaccines, these guidelines provide sound recommendations that are in many ways applicable to the environmental release of live vaccines. Depending on the vaccine microorganism and the proposed target environment, the following guidelines are used by VB in the risk management phase: the Organization for Economic Co-Operation and Development (OECD) Good Developmental Practices for Small Scale Field Research with Genetically Modified Plants and Micro-Organisms (5); the OECD Safety Considerations for Biotechnology (6); the National Research Council Report, Field Testing of Genetically Modified Organisms, a Framework for Decisions (7); and the Royal Commission on Environmental Pollution Report, The Release of Genetically Engineered Organisms to the Environment (8).

V. Risk Communication

Risk communication is the last phase of the risk analysis process. The goal is to communicate to the public the safety risks associated with the proposed action. The public for veterinary biological products includes scientists, the regulated industry, professional organizations, government agencies, public interest groups, and individual citizens. Emphasis is placed on communicating safety risks to individuals who may be interested or affected by the actions taken by VB, APHIS. Because these individuals often have distinct interests, objectives, and background, risk communication is a complex, sensitive, and time consuming enterprise. Notwithstanding, risk communication is paramount to the success of the risk analysis process. Further, public involvement is required of all Federal agencies that implement procedures or take actions subject to NEPA.

VB procedures for communicating risk are summarized in Figure 2 (Page 18). These procedures provide several options for communicating risk. Risk assessments and environmental documents are made available to the public before decisions are made and actions are taken. VB procedures for communicating risk include reviews by scientists outside APHIS. The integrity of Confidential Business Information (CBI) is ensured by requiring reviewers to sign an Authorized User Certificate for Handling CBI (see Appendix H, Page 35). The selection of reviewers is subject to approval by the applicant. Unless the proposed action is exempt due to categorical exclusion, VB prepares either an Environmental Assessment or Environmental Impact Statement. Depending on the risk rating, and the level of uncertainty, the risk assessment conducted by VB is subject to either a standard or special review.

A. Standard Review

When it is determined from the risk assessment that the safety risk to animals, public health, and the environment is low, and therefore of acceptable risk; standard procedures for communicating risk are implemented.

1. Peer Review

VB convenes an Ad Hoc Expert Panel to review the risk assessment and the associated risk management recommendations. The panel consists of representatives from Federal agencies, academic institutions, and professional societies. Panel members are chosen for their expertise with the parent microorganism (from which the vaccine microorganism was derived).

If public health concerns are identified in the risk assessment, an official position is requested from the Health and Human Services (HHS) Department through the existing Memorandum of Understanding with the National Vaccine Program Office (NVPO). The NVPO convenes a subcommittee of public health specialists that are chosen for their expertise with the vaccine microorganism (e.g., the Vaccinia Subcommittee). An additional review by an Ad Hoc Expert Panel is not required.

2. Public Notification

a. Environmental assessment (FONSI)

An Environmental Assessment is a succinct document that briefly provides sufficient evidence and analysis for determining whether to prepare an Environmental Impact Statement or a Finding of No Significant Impact (FONSI). Each Environmental Assessment contains background information; a brief discussion of the need for the proposed action; a discussion of safety risks to animals, public health, and the environment; alternatives, as required by section

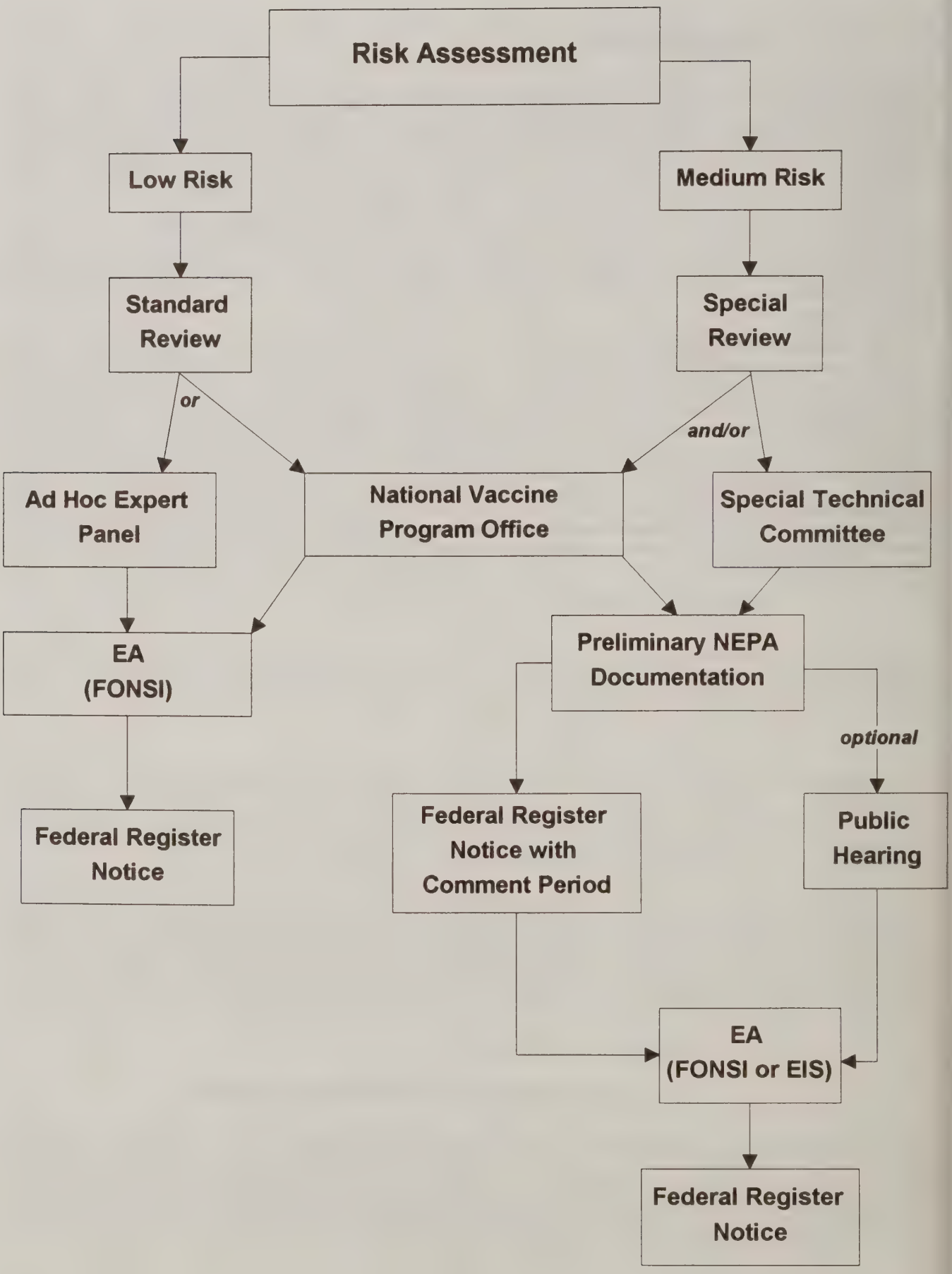

Figure 2: Procedures For Communicating Risk

102(2)(E) of NEPA; and a list of Federal Agencies and persons consulted.

If the Ad Hoc Expert Panel or the NVPO agrees with the risk ratings of the risk assessment, VB prepares an Environmental Assessment. When the risk ratings are low VB determines that implementation of the proposal will not significantly affect the quality of the human environment (FONSI), and that the preparation of an Environmental Impact Statement is not required.

b. Federal Register Notice

The availability of the Environmental Assessment and FONSI is publicly announced in the Federal Register Notice without a comment period. The proposed action is approved concurrently with the Federal Register announcement.

B. Special Review

1. Peer Review

If it is determined from the risk assessment that the risk is medium, and therefore unacceptable without adequate procedures to mitigate the risk, VB convenes a Special Technical Committee. Similar to an Ad Hoc Expert Panel, the committee consists of representatives from Federal agencies, academic institutions, and professional societies. However, the committee members have specific expertise in the areas of concern raised in the risk assessment. If the area of concern is public health, an official position is requested from the NVPO. If other areas of concern are raised in addition to public health (e.g., environmental safety), a Special Technical Committee may also be convened to address those issues.

2. Public Notification

a. Preliminary NEPA Documentation

A preliminary Environmental Assessment, FONSI, or EIS is prepared.

b. Public Hearing

If the proposed action pertains to a specific geographical location, APHIS may organize a public hearing. Substantive comments from the public hearing are reviewed and included in the risk assessment.

c. Federal Register Notice

The availability of the Environmental Assessment and preliminary FONSI is publicly announced in the Federal Register Notice with a 30-day comment period. If the 30-day comment period produces substantive comments, VB must provide an adequate response. If VB does not have adequate information to respond, additional information or data may be required from the applicant. The risk analysis process may also be repeated.

d. Environmental assessment (FONSI) or EIS

VB prepares an Environmental Assessment and FONSI. Thus, VB determines that implementation of the proposal will not significantly affect the quality of the human environment (FONSI) and that the preparation of an Environmental Impact Statement is not required.

e. Federal Register Notice

The availability of the Environmental Assessment is publicly announced in the Federal Register Notice with a comment period. The proposed action is approved concurrently with the Federal Register announcement.

C. Public Access to Federal Decision-Making Information

All documents related to the review process are public documents and are available to the public, pursuant with the provisions of the Freedom of Information Act (FOIA). Information in the possession and control of APHIS that qualifies as a record and that is not exempt from disclosure under FOIA is made available upon written request. This includes interagency memoranda, where such memoranda transmit comments on the environmental impact of the proposed action, and NEPA documents. Confidential business information (CBI), as defined by FOIA, is exempt. Thus, risk analyses are made available to the public after CBI has been removed. Materials made available to the public are provided without charge to the extent practical, or at a fee that is not more than the actual costs of reproducing copies [in accordance with 40 CFR 1506.6.(f)]. The public should submit requests for information directly to the FOIA Office:

U.S. Department of Agriculture
APHIS, Freedom of Information
6505 Belcrest Road, Room 600 FB
Hyattsville, MD 20782

VI. Summary

The risk analysis presented in this document provides a systematic interdisciplinary approach for conducting risk assessments. This process ensures the use of scientific information in planning and decision-making. The risk analysis for veterinary biologics is flexible but comprehensive. The likelihood of an adverse event and the consequences if that adverse event occurs are taken into consideration. Because safety studies are required for licensing veterinary biologics, risk decisions are based on empirical data. Information from the appropriate scientific literature is used when empirical data are not available. Thus, the degree of certainty for each risk rating is fairly high. This permits the characterization of safety risks that are based on a qualitative assessment.

Although the risk analysis for veterinary biologics was designed specifically to ensure the safety of experimental veterinary vaccines, the model lends itself to other risk issues fairly easily. Summary information formats can be developed for different products or regulatory issues. If necessary, the model can incorporate quantitative analyses when the degree of certainty is low. For instance, the likelihood of an adverse event can be assessed quantitatively. However, the assignment of the final risk rating must include, in addition to the likelihood, the consequence of the adverse event.

The risk analysis for veterinary biologics has been used to evaluate several field tests. Examples of these risk analyses are provided in Appendix I (Page 36). Some of the analyses have undergone peer review by NVPO and other ad hoc expert panels. Although the results of these reviews have been favorable (i.e., outside reviewers have agreed with the assigned risk ratings and the conclusions of the risk analyses), any disparity or suggested changes are welcome. This ensures an open process and the continuing improvement of the VB risk analysis process.

VII. References

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5. Organization for Economic Co-Operation and Development (OECD). (1992). Safety Considerations for Biotechnology, Paris.

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9. Biosafety in Microbiological and Biomedical Laboratories, HHS Publication No. (NIH) 88-8395, 2nd ed. (1988).

10. Guidelines for Research Involving Recombinant DNA Molecules, FR 51: 16957-1698

VIII. Appendices

APPENDIX A

SUMMARY INFORMATION FORMAT FOR VETERINARY BIOLOGICS

I. INTRODUCTION
   A. Objective
   B. Proposal

II. CHARACTERIZATION OF THE VACCINE MICROORGANISM
   A. Microbiological Properties

      1. Parental microorganism:

         (a) Identity of parental strain:
         (b) Genetic markers:

      2. Development of the vaccine strain:

         (a) Procedures used to attenuate the parental strain:
         (b) Screening methods and protocols for the identification and purification of the vaccine microorganism:
         (c) Vaccine production:

      3. Characterization of the Master Seed:

         (a) Master Seed designation:
         (b) Method(s) and protocols used to establish identification of the Master Seed:
         (c) Stability of the Master Seed microorganism at the n and n+5 (highest passage level):

   B. Biological Properties

      1. Parental microorganism:
         (a) Virulence:
         (b) Tissue tropism in susceptible host(s):
         (c) Horizontal gene transfer/recombination potential:
         (d) Host/Range specificity:
         (e) Shed/Spread capabilities:
         (f) Environmental distribution:
         (g) Geographical distribution:
         (g) Recommended NIH/CDC biosafety levels:

      2. Master Seed:
         (a) Virulence:
            (i) Target animal:
            (ii) Non-Target animals:
         (b) Purity:
         (c) Phenotypic stability:
         (d) Tissue tropism in susceptible host(s):
         (e) Horizontal gene transfer/recombination potential:
         (f) Shed/Spread capabilities:
         (g) Host/Range specificity:
         (h) Effect of overdosing:
         (e) Survivability of the microorganism in the environment:
         (g) Environmental distribution:

APPENDIX B

SUMMARY INFORMATION FORMAT FOR CATEGORY I VETERINARY BIOLOGICS

I. INTRODUCTION

A. Objective
B. Proposal

II. CHARACTERIZATION OF THE RECOMBINANT MICROORGANISM

A. Molecular Properties

1. Recipient characterization:

(a) Parental organism:
(b) Description of the recipient organism prior to receiving the deletion(s) and/or donor gene:
(c) Genetic modifications used to produce the recipient organism from the parental organism:

2. Characterization of the deletion(s), where applicable:

(a) Deleted gene(s):
(b) Proposed phenotypic effect of the deletion(s) upon the recipient organism:

3. Characterization of the donor gene(s), where applicable:

(a) Donor organism:
(b) Donor gene(s), including any inserted marker genes:

4. Construction of the recombinant organism:

(a) Summary of the construction process:
(b) Intermediate cloning vector(s):
(c) Procedure for introducing the genetic modification(s) to the recipient:
(d) Procedure for introducing the genetic modification(s) to the donor genes:
(e) Screening methods and protocols for the identification and purification of the recombinant organism:

5. Molecular characterization of the Master Seed:

(a) Master Seed designation:
(b) Method(s) and protocols used to establish identification of the Master Seed:
(c) Stability of the Master Seed organism at the n and n+5 (highest passage level):

B. Biological Properties

1. Recipient:

(a) Virulence:
(b) Biological effect of the genetic manipulation at the

cloning site(s):
(c) Tissue tropism in susceptible host(s):
(d) Horizontal gene transfer/recombination:
(e) Host/range specificity:
(f) Environmental distribution:
(g) Geographical distribution:
(h) Recommended NIH/CDC biosafety levels:

2. Donor(s):

(a) Virulence:
(b) Biological function encoded by the donor gene(s):
(c) Previous safe use of donor genes:
(d) Tissue tropism in susceptible host(s):
(e) Horizontal gene transfer:
(f) Host/range specificity:
(g) Pathogenic or toxic properties of the donor gene(s):
(h) Ability of the donor gene(s) to produce resistance to therapeutic agents:
(i) Recommended NIH/CDC biosafety level:

3. Master Seed:

(a) Purity:
(b) Inactivation and monitoring procedures:

APPENDIX C

SUMMARY INFORMATION FORMAT FOR CATEGORY II VETERINARY BIOLOGICS

I. INTRODUCTION

A. Objective
B. Proposal

II. CHARACTERIZATION OF THE GENE-DELETED MICROORGANISM

A. Molecular Properties

1. Recipient characterization:

(a) Parental organism:
(b) Description of the recipient organism prior to receiving the deletion(s):
(c) Genetic modifications used to produce the recipient organism from the parental organism:
(d) Genetic markers:

2. Characterization of the deletion(s):

(a) Deleted gene(s):
(b) Proposed phenotypic effect of the deletion(s) upon the recipient organism:
(c) Identity and properties of the inserted marker gene(s):

3. Construction of the gene-deleted organism:

(a) Summary of the construction process:
(b) Intermediate cloning vector(s):
(c) Procedure for introducing the genetic modification(s) to the recipient:
(d) Procedure for introducing any inserted marker genes:
(e) Screening methods and protocols for the identification and purification of the gene-deleted organism:

4. Molecular characterization of the Master Seed:

(a) Master Seed designation:
(b) Method(s) and protocols used to establish identification of the Master Seed:
(c) Stability of the Master Seed organism at the n and n+5 (highest passage level):

B. Biological Properties

1. Recipient:

(a) Virulence:
(b) Previous use of the recipient organism:
(c) Tissue tropism in susceptible host(s):

(d) Horizontal gene transfer/recombination potential:
(e) Host/Range specificity:
(f) Environmental distribution:
(g) Geographical distribution:
(h) Recommended NIH/CDC biosafety levels:

2. Master Seed:

(a) Virulence:
    (i) Target animal:
    (ii) Non-Target animals:
(b) Biological effect of the genetic modification(s):
    (i) Phenotypic effect of the gene deletion(s):
    (ii) Previous use of the microorganism containing the gene deletion(s):
    (iii) Phenotypic effect of any genetic marker(s):
(c) Purity:
(d) Genetic stability:
(e) Phenotypic stability:
(f) Tissue tropism in susceptible host(s):
(g) Horizontal gene transfer/recombination potential:
(h) Shed/Spread capabilities:
(i) Host/Range specificity:
(j) Effect of overdosing:
(k) Survivability of the microorganism in the environment:
(l) Environmental distribution:

APPENDIX D

SUMMARY INFORMATION FORMAT FOR CATEGORY III VETERINARY BIOLOGICS

I. INTRODUCTION

A. Objective
B. Proposal

II. CHARACTERIZATION OF THE RECOMBINANT VECTOR

A. Molecular Properties

1. Recipient characterization:

(a) Parental organism:
(b) Description of the recipient organism:
(c) Genetic modifications used to produce the recipient organism from the parental organism:
(d) Cloning site(s):
(e) Identity of the gene(s) located at the cloning site:
(f) Genetic markers:

2. Donor characterization:

(a) Donor organism(s):
(b) Donor gene(s):
(c) Proposed phenotypic effect of the donor construct(s) in the recombinant organism:

3. Construction of the recombinant organism:

(a) Summary of the construction process:
(b) Intermediate cloning vector(s):
(c) Procedure for introducing the genetic modification(s) to the recipient:
(d) Procedure for introducing the genetic modification(s) to the donor genes:
(e) Screening methods and protocols for the identification and purification of the recombinant organism:

4. Molecular characterization of the Master Seed:

(a) Master Seed designation:
(b) Method(s) and protocols used to establish identification of the Master Seed:
(c) Stability of the Master Seed organism at the n and n+5 (highest passage level):

B. Biological Properties

1. Recipient:

(a) Virulence:
(b) Previous use of the recipient organism:
(c) Tissue tropism in susceptible host(s):
(d) Horizontal gene transfer/recombination potential:
(e) Host/Range specificity:

(f) Environmental distribution:
(g) Geographical distribution:
(h) Recommended NIH/CDC biosafety levels:

2. Donor(s):

(a) Virulence:
(b) Biological function encoded by the donor gene(s):
(c) Previous use of donor gene(s):
(d) Tissue tropism in susceptible host(s):
(e) Horizontal gene transfer/recombination potential:
(f) Host/Range specificity:
(g) Pathogenic or toxic properties of the donor gene(s):
(h) Ability of the donor genes to produce resistance to therapeutic agents:
(i) Recommended NIH/CDC biosafety level:

3. Master Seed:

(a) Virulence:
    (i) Target animal:
    (ii) Non-Target animals:
(b) Biological effect of the genetic modification at the cloning site(s):
    (i) Biological function encoded by the gene(s) at the cloning site:
    (ii) Previous safe use of cloning site(s):
(c) Purity:
(d) Genetic stability:
(e) Phenotypic stability:
(f) Tissue tropism in susceptible host(s):
(g) Horizontal gene transfer/recombination potential:
(h) Shed/Spread capabilities:
(i) Host/Range specificity:
(j) Effect of overdosing:
(k) Survivability of the microorganism in the environment:
(l) Environmental distribution:

APPENDIX E

HAZARD IDENTIFICATION FOR VETERINARY BIOLOGICS

I. ANIMAL SAFETY

A. Target Animal Safety

1. Vaccination
2. Vaccination/Challenge
3. Reversion to virulence
4. Purity testing
5. Effect of gene manipulation on pathogenicity
6. Genetic stability
7. Phenotypic stability
8. Alteration of tissue tropism
9. Effect of overdosing

B. Non-Target Animal Safety

1. Probability of non-target animal exposure
2. Virulence in non-target animals
3. Possible outcome of non-target animal exposure

II. PUBLIC HEALTH SAFETY

A. Probability of Human Exposure

B. Pathogenicity of the Parent Microorganism in Humans

C. Virulence of the Vaccine Microorganism in Humans

D. Possible Outcome of Human Exposure

III. ENVIRONMENTAL SAFETY

A. Shed/Spread Capabilities

B. Horizontal Gene Transmission/Recombination Potential

C. Host/Range Specificity

D. Survivability of the Microorganism in the Environment

E. Potential for Transmission to Invertebrates

F. Physical and/or Chemical Factors Affecting Dispersal in the Environment

G. Adverse Ecological Effects

APPENDIX F

SUMMARY INFORMATION FORMAT FOR CONTAINED STUDIES

I. INTRODUCTION

A. Objective
B. Proposal

II. CONTAINED STUDY

A. Location of animal facilities

Identify the exact location of the animal facilities. A description of the area surrounding the animal facilities should be provided, including the presence of non-target animal species.

B. Characteristics of animal facilities

Provide a comprehensive description of the facilities, including blueprints and legends, containment equipment, air flow, autoclaves, incinerators, etc. Identify the biosafety levels assigned to the facilities for the proposed study. The facilities should be certified by the local Institutional Biosafety Committee (IBC).

C. Personnel

Identify the personnel conducting the study, including their qualifications and training in biosafety. Identify appropriate safeguards, such as vaccination, protective clothing, and protective gear are provided.

D. Protocol of study

The protocol of study should identify the operational procedures for the assigned biosafety level. The following information should be provided: 1) the number of animals; 2) the route of administration; 3) the dose; 4) the total amount of test material; 5) the method of disposing waste; 6) protective apparel and equipment for the individuals conducting the study.

E. Potential for an environmental release

The potential for escapes from the contained animal facilities should be assessed. Possible exposure to the area surrounding the animal facilities should be considered and documented.

F. Monitoring

Monitoring methods to distinguish the vaccine microorganism from the parental or other microorganisms should be identified. The frequency and effectiveness of monitoring procedures should be determined prior to initiating the study.

APPENDIX G

SUMMARY INFORMATION FORMAT FOR ENVIRONMENTAL RELEASES

I. INTRODUCTION

A. Objective
B. Proposal

II. ENVIRONMENTAL RELEASE

A. Location of test site

Identify the exact location of the test site. For proposed commercial uses, the conditions under which the vaccine will be used should be identified; e.g., unlimited commercial distribution and use, restricted for use by veterinarians only, small animal veterinary hospitals, commercial poultry houses, etc.

B. Characteristics of the test site

Identify the size of the test site, including relevant geographical and environmental information. A description of the area surrounding the test site should be provided, including the presence of non-target animal species. The condition of the test site should be documented, as well as previous studies conducted on the test site.

C. Personnel

Identify the personnel conducting the study, including their qualifications, training, and specific role in the study. Appropriate safeguards, education, and training should be provided as needed.

D. Experimental design

Identify the objectives of the release. For small-scale field tests, the protocol of study should include the following information, as appropriate: 1) the number of animals; 2) a description of the animals; 3) the route of administration; 4) the dose; 5) the total amount of test material; 6) frequency and duration of exposure; 7) the method of disposing waste; 8) decontamination of the test site.

VB recommends the application of Good Developmental Practices (GDP) in the design of the study. These guidelines were specifically devised by the Organization for Economic Co-Operation and Development (OECD) for small-scale field research with genetically modified plants and microorganisms. The GDP concept is applicable to field tests conducted with vaccine microorganisms. The goal is to design an experiment that will minimize the dissemination of the microorganism, and control the transfer of heterologous genetic material.

E. Potential for escape and dispersal in the environment

The potential for escape and dispersal from the release site should be assessed. Possible exposure to the area surrounding the test site should be considered and evaluated, including the probability of non-target animal exposure.

F. Potential for establishment in the environment

The habitability of the test site and/or environments for the introduced vaccine microorganism is appraised. The following environmental characteristics are evaluated, as appropriate: 1) the presence of other biological organisms; 2) the nutrient status; 3) physicochemical factors; 4) the presence of toxic chemicals and metabolites.

G. Monitoring

Environmental monitoring is crucial for the success of the risk analysis process; monitoring is an essential part of ensuring that unacceptable or unexpected adverse events do not occur. Thus, appropriate methods and procedures for monitoring the released vaccine microorganism in and around the test site should be identified prior to initiating the study. The monitoring methods should be sensitive and specific. Provisions for recording the results of the monitoring should be in place.

H. Contingency plans in case of adverse event

The sponsor of the proposed study should identify contingency plans in case an adverse event occurs. Contingency plans should include procedures for terminating the study as quickly as possible, and identify methods to stop the shed, spread, or dispersal of the vaccine microorganism once released in the environment.

APPENDIX H

U.S. DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

AUTHORIZED USER CERTIFICATION FOR HANDLING CONFIDENTIAL BUSINESS INFORMATION

As a condition of serving as an authorized user for the handling of confidential business information (CBI), I, _____ hereby certify that I am familiar with the provisions

(Print or Type)

of the Animal and Plant Health Inspection Service (APHIS) Policy Statement on the Protection of Privileged or Confidential Business Information (50 FR 38561-38563), concerning requirements to control and protect documents that contain privileged or CBI. I further certify that I will not engage in any conduct contrary to those provisions set forth in the aforementioned policy statement.

The provisions of the policy statement have been made available to me.
I understand the continuing obligation to comply with the policy statement, and to keep all information submitted to me by APHIS confidential for a period of 5 years. Upon termination of my status as an authorized user, all CBI documents that were provided to me shall be returned.

_____ _____

Date Signature of Authorized User

_____ _____

Agency Position and Office Location

APPENDIX I

Examples of Risk Analyses Conducted for Veterinary Biologics

Name of Vaccine	Purpose
Pseudorabies Vaccine, Modified Live Virus	Environmental Release
Salmonella Choleraesuis Vaccine, Avirulent Live Culture	Environmental Release
Rabies Vaccine, Vaccinia Vector	Environmental Release
Toxoplasmosis Vaccine, Live Protozoa	Environmental Release
Newcastle Disease-Fowl Pox Vaccine, Fowl Pox Vector	Environmental Release
Rinderpest Vaccine, Vaccinia Vector	Contained Study